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10/507,466	09/10/2004	Marc Ostermeier	56908(71699)	1259

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,466	OSTERMEIER, MARC	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,8,14 and 45-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 8, 14 and 45-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 11-21-08 has been entered. Claims 1, 7, 14, 45 and 46 have been amended. Claims 1-5, 7, 8, 14 and 45-47 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 45-47 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and is repeated for the reasons set forth in the preceding Official action mailed 5-29-08. Applicant's arguments filed 11-21-08 have been fully considered but they are not persuasive.

Applicant argues that claim 45 has been amended to recite inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence and paragraphs [0021], [0130], [0139], [0140], [0131], [0177], [0216] and [0217] provide support for the phrase at issue (amendment, p. 12-13). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-08. Those paragraphs only disclose different nuclease treatment or combination thereof, or other types of treatment including mechanical shearing, chemical treatment, and/or radiation. However, those cited paragraphs fails to provide sufficient support for "**one or more** of a method selected from nuclease treatment, mechanical sheering,

chemical treatment or radiation treatment". There is no support in the specification for the combination of one or more method selected from nuclease treatment, mechanical sheering, chemical treatment and radiation treatment. Thus, the claims remain rejected under 35 U.S.C. 112 first paragraph.

3. Claims 45-47 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vitro, does not reasonably provide enablement for treating a nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vivo, or for treating any molecule other than nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vitro or in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 5-29-08. Applicant's arguments filed 11-21-08 have been fully considered but they are not persuasive.

Applicant argues that claim 45 has been amended to recite inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence carried out by one or more of a method selected from nuclease treatment, mechanical sheering, chemical treatment or radiation treatment (amendment, p. 13-14). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-08. Claims 45-47 read on inserting any molecule randomly into another molecule and the inserting randomly comprises one or more of a method selected from nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical

sheering, chemical treatment or radiation treatment in vitro or in vivo. The specification only discloses treating nucleic acid with nuclease treatment, such as 3' to 5' exonuclease digestion, mechanical sheering, chemical treatment or radiation treatment. The specification fails to provide adequate guidance and evidence for how to treat a nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vivo, how to prepare randomly linearized insertion sequence and acceptor sequences with nuclease, mechanical shearing, chemicals or radiation in a cell in vivo and how to perform random insertion of an insertion sequence into an acceptor sequence in vivo. The claims encompass any target cell at numerous different locations in a subject. There are various barriers before a outside agent can reach its target cells, for example, skin cells, muscle cells, layers of dermal cells, blood vessel wall cell membranes, nucleases, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids. There is no evidence of record that demonstrates treating a nucleic acid, including insertion sequence and acceptor sequence, with nuclease, mechanical shearing, chemicals or radiation in vivo, and performing random insertion of an insertion sequence into an acceptor sequence in vivo. Absent specific guidance, one skilled in the art at the time of the invention would not know how to practice the full scope of the invention claimed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-5, 7, 8 and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Lacatena et al., 1994 (PNAS, Vol. 91, pp. 10521-10525) and is repeated for the reasons set forth in the preceding Official action mailed 5-29-08. Applicant's arguments filed 11-21-08 have been fully considered but they are not persuasive.

Applicant argues that the Lacatena reference does not teach or suggest assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state, such as an activity (amendment, p. 15-16). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-08. Generation of the hubeta2AR-phoA fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. PhoA can be considered as an insertion sequence and the hubeta2AR (human beta2-adrenergic receptor) protein can be considered as an acceptor sequence. PhoA encodes bacterial alkaline phosphatase and hubeta2AR encodes human beta2-adrenergic receptor. The state of alkaline phosphatase is coupled to the state of the human beta2-adrenergic receptor and the fusion protein comprises a state. Lacatena teaches assaying the alkaline phosphatase activity of the fusion protein. A fusion protein can respond to a

stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. Thus, the claims remain anticipated by Lacatena.

6. Claims 1-5, 7, 8 and 14 remain rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., 2003 (US Patent No. 6,596,485 B2) and is repeated for the reasons set forth in the preceding Official action mailed 5-29-08. Applicant's arguments filed 11-21-08 have been fully considered but they are not persuasive.

Applicant argues that Anderson reference does not teach each comprise a state such that the state of one is coupled to the state of another such that a measurable change in the other state is observed. Anderson does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 16-17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-08. Anderson teaches fusing random peptide into GFP to generate GFP fusion protein via insertion of nucleic acid. The random peptide is fused to an internal position of the GFP and the peptide can be inserted at virtually any position but preferred positions include insertion at the very tips of loops on the surface of the GFP (e.g. column 17, lines 1-38). Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The peptide can be considered as an insertion sequence and the GFP can be considered as an acceptor sequence, which can have a deletion, a substitution or insertion. The inducible promoter, such as Tet

regulatory element, is responsive to inducer, such as tetracycline. When inducer, such as tetracycline, is present, the fusion molecule (fusion nucleic acid operably linked to the inducible promoter) switches state in response to the signal (the inducer, such as tetracycline), which is a measurable change. Further, a fusion protein can respond to a stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. Thus, the claims remain anticipated by Anderson.

7. Claims 1-5, 7, 8 and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Manoil et al., 1990 (Journal of Bacteriology, Vol. 172, No. 2, p. 515-518) and is repeated for the reasons set forth in the preceding Official action mailed 5-29-08. Applicant's arguments filed 11-21-08 have been fully considered but they are not persuasive.

Applicant argues that the Manoil reference does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-08. The insertion of TnphoA into a gene (transposon insertion) is random and the fusion gene encoding hybrid proteins with alkaline phosphatase activity are detected as blue colonies on media containing the alkaline phosphatase indicator dye (e.g. p. 515, right column). Generation of the hybrid proteins constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The resulting hybrid protein or gene encoding said hybrid protein is a new state. A fusion protein can

respond to a stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. Thus, the claims remain anticipated by Manoil.

8. Claims 1-5, 7, 8 and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Mountford et al., 1995 (TIG, Vol. 11, No. 5, p. 179-184) and is repeated for the reasons set forth in the preceding Official action mailed 5-29-08. Applicant's arguments filed 11-21-08 have been fully considered but they are not persuasive.

Applicant argues that the Mountford reference does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-08. Mountford teaches gene trapping for identifying developmentally regulated genes based on the random integration of a reporter into chromosomal transcription units. Mountford further teaches that IRES-containing gene trap construct pGT1.8Iresbetageo enhances frequency of productive integration as compared to control vector (e.g. p. 182, right column). The gene trap vector is an insertion sequence and the choromosomal transcription units are acceptor sequences. The gene trap vector encodes betagal protein and the chromosomal transcription unit encodes another protein. The resulting fusion molecule is a new state. A fusion protein can respond to a stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. Thus, the claims remain anticipated by Mountford.

9. Claims 1-5, 7, 8 and 14 remain rejected under 35 U.S.C. 102(e) as being anticipated by Ong, Christopher, 2005 (US Patent No. 6,867,035 B2) and is repeated for the reasons set forth in the preceding Official action mailed 5-29-08. Applicant's arguments filed 11-21-08 have been fully considered but they are not persuasive.

Applicant argues that the Ong reference does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 18). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-08. Ong teaches preparation of gene trap DNA construct comprising a mutagenic, detectable component containing a IRES linked to a reporter gene and a functional unit comprising a reporter gene under the control of PGK promoter. Transfection of the gene trap construct via electroporation into ES cells results in random integration into ES cell genome by illegitimate recombination. The gene trap DNA construct is an insertion sequence and the ES cell genome is acceptor sequence. The gene trap DNA encodes a reporter and the trapped gene in ES cell genome encodes another protein. The resulting fusion molecule is a new state. A fusion protein can respond to a stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. Thus, the claims remain anticipated by Ong.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1 and 45-47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., 2003 (US Patent No. 6,596,485 B2) in view of Norris, 2006 (US Patent No. 7,135,176) and is repeated for the reasons set forth in the preceding Official action mailed 5-29-08. Applicant's arguments filed 11-21-08 have been fully considered but they are not persuasive.

Applicant argues that Anderson or Norris reference does not assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 18-19). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 5-29-08 and the reasons set forth above under 35 U.S.C. 102(e) rejection in view of Anderson reference. Although Norris does not teach assembling a modulatable molecule, however, Anderson does teach how to assemble a modulatable molecule as claimed. Thus, the claims remain rejected under 35 U.S.C. 103(a).

Conclusion

No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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